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Studies of Carcinogenicity of Sodium Chlorite in B6C3F1 Mice

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The carcinogenic activities of sodium chlorite in B6C3F1 mice were examined. Sodium chlorite was given at concentrations of 0 (control), 0.025% (low dose), or 0.05% (high dose) in the drinking water of 150 female and 150 male mice for 80 weeks, after which time the animals were returned to distilled water without sodium chlorite. All mice were sacrificed 85 weeks from the beginning of the experiment. The incidence of tumor-bearing animals was 32% (control), 34% (low dose), and 26% (high dose) in female mice, and 46% (control), 57% (low dose), and 53% (high dose) in male mice. The types and incidence of neoplasms that occurred frequently in each group of both sexes were similar to those observed spontaneously in B6C3F1 mice. The incidence of lymphomas/leukemias in the high dose group of females (2%), however, was lower than that in the control group (15%). Furthermore, the incidence of pulmonary adenomas in the high dose group of males (12%) was higher than that in the control group (0%), but neither dose-related increases in the adenoma incidences nor increased incidences of the adenocarcinomas were observed. These results indicated no clear evidence of a carcinogenic potential of sodium chlorite in B6C3F1 mice.

Introduction

Since 1958, sodium chlorite has been used in Japan (*1*) as a bleaching agent for cherry, grape, peach, and butterbur in the process of preservation in sugar. In the United States, the primary method of water disinfection uses chlorine. However, it has become clear that chlorine interacts with organics in the water to form trihalomethanes such as chloroform, bromodichloromethane, dibromochloromethane, and bromoform (*2*). Chloroform has been shown to be carcinogenic in mice and rats (*3*). It has also been postulated that chlorinated water supplies may increase the risk of cancer in humans (*4–7*). From these observations, chlorine dioxide was suggested as an attractive alternative disinfectant. Chlorine dioxide does not form trihalomethanes, but it forms chlorite and chlorate as by-products in concentrations of 50% and 30% of its demand, respectively (*8*). While toxicological studies have revealed limited physiologic effects from chlorine dioxide, oral acute doses of sodium chlorate have resulted in hemolysis, nephritis, methemoglobinemia, and death in man and various species of test animals (*9*). Based on these findings, a number of acute and chronic toxicological studies on chlorite were performed in laboratory animals (*10–13*), since chlorite is thought to be the most potentially toxic by-product (*14,15*).

Recently, a potential promoting effect of sodium chlorite was suspected in two-stage skin carcinogenesis using female Sencar mice (*16*). In another study, it had been shown that sodium chlorite was positive in both Ames tests and chromosome tests (*17*). TR values calculated in the chromosome test, which indicates the frequency of cells with exchange-type aberrations per unit dose (mg/mL), were high (*17*), indicating that sodium chlorite may possess carcinogenic potential in animals (*18*). This paper reports the results of a long-term carcinogenicity testing of sodium chlorite in B6C3F1 mice.

Materials and Methods

Chemicals

Sodium chlorite was obtained from Wako Pure Chemical Industries, Ltd. (Kyoto, Japan) in a single batch (purity 82–87%) and was administered orally to animals in drinking water at various concentrations mentioned below. The drinking water was prepared and supplied fresh three times a week in light-proof bottles.

Animals and Maintenance

Three hundred B6C3F1 mice (150 females and 150 males) were purchased from Shizuoka Laboratory Cen-

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ter (Shizuoka, Japan). Mice were given a pellet diet (CRF-1; Charles River Japan, Inc., Kanagawa, Japan) *ad libitum*. The mice were 6 weeks old at the beginning of the experiment and were housed five to six in plastic cages, with wood chips as bedding. The room temperature was kept at 23 ± 2°C and the humidity at 55 ± 10%, with a 12-hr light/dark cycle.

Experimental Procedure

Groups of 50 mice of each sex were given the sodium chlorite solution at a concentration of 0 (control), 0.025% (low dose), or 0.05% (high dose) for 80 weeks followed by distilled water alone for another 5 weeks. The high dose was chosen after a preliminary 13-week subacute toxicity study. In the subacute toxicity study, nine doses of sodium chlorite, 0, 0.00625, 0.0125, 0.025, 0.05, 0.1, 0.25, 0.5, and 1% in drinking water, were used. Mice given higher doses than 0.25% died of dehydration due to a strong smell of the sodium chlorite-containing water. The dose of 0.1% exerted 7% and 6% growth retardation in female and male mice, respectively. The dose of 0.05% exerted, respectively, 2% and 4% growth retardation in females and males. Because of a narrow tolerance range between the doses of 0.1% and 0.25%, we selected the dose of 0.05% as the highest dose for long-term carcinogenicity studies of sodium chlorite. According to the guideline for carcinogenicity studies from the Ministry of Health and Welfare of Japan, the test compound was withdrawn for the final 5 weeks. The withdrawal may further progress the induced tumor growth or regress reversible proliferative lesions, which makes a histological evaluation of test compounds easier. The animals were observed daily for abnormalities. Individual body weights were recorded weekly for the first 13 weeks and every other week thereafter. Water consumption was measured over the 1-day period before each weighing.

After 85 weeks, surviving animals were deprived of food, but not water, overnight and then killed under ether anesthesia by exsanguination from the aorta. Peripheral blood was taken from each mouse for the microscopical examination by Giemsa stain.

Gross findings were recorded and the following organs of each mouse were weighed: brain, heart, lung, liver, pancreas, spleen, kidney, adrenals, and testes or ovaries. Samples of these organs and of salivary gland, trachea, thymus, lymph nodes, stomach, small intestine, large intestine, urinary bladder, pituitary, thyroid, prostate, seminal vesicle, uterus, vagina, mammary gland, skeletal muscle, eye, Harderian glands, spinal cord, bone (sternal bone, ribs, vertebral bone), and other tissues with abnormal appearance were fixed in 10% neutralized formalin. Preserved tissues to be examined microscopically were embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin (HE). Histopathological examinations were also performed on mice found dead and those in moribund condition when killed.

Statistical Analyses

Data on cumulative mortality and tumor incidence were analyzed for statistical significance by the chi-square test.

Results

Body Weights

Growth curves of female and male mice are shown in Figures 1 and 2. Female mice of each group gained body weight up to 60 weeks; however, thereafter, the mice given a high dose of sodium chlorite showed a decrease in body weight gain compared to other groups. Male mice of each group showed a decrease in body weight after 65 weeks. Final body weights of female and male mice showed no significant differences among each group.

Water Consumption

Throughout the study, the rate of water consumption by female mice in any group treated with sodium chlorite showed no consistent deviation from the control. On the other hand, water consumption by male mice treated with a high dose of sodium chlorite was slightly lower than the other groups. For treated groups, total intakes of sodium chlorite for 80 weeks, calculated from mean water consumption collected on 46 different days during

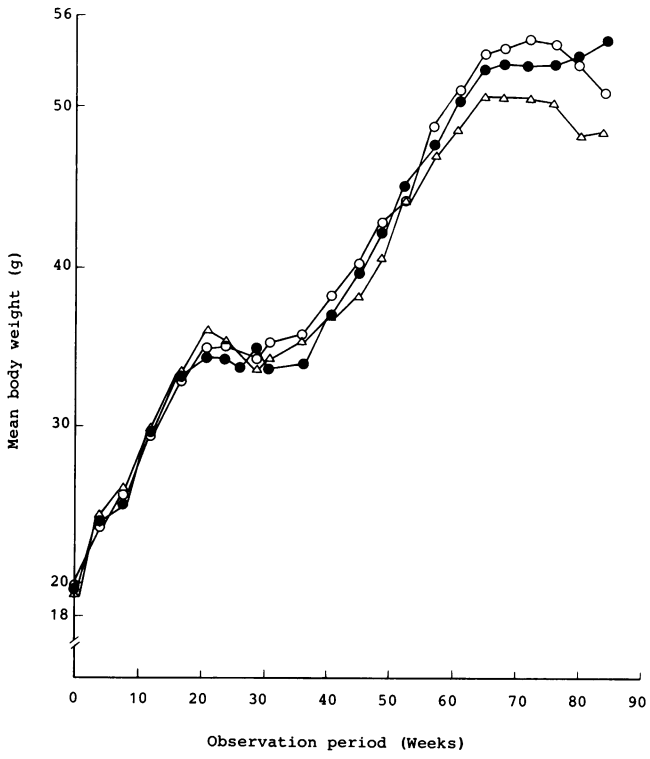

FIGURE 1. Growth curves of female B6C3F1 mice given sodium chlorite in drinking water at concentrations of 0 (control) (○—○), 0.025 (●—●), or 0.05% (△—△).

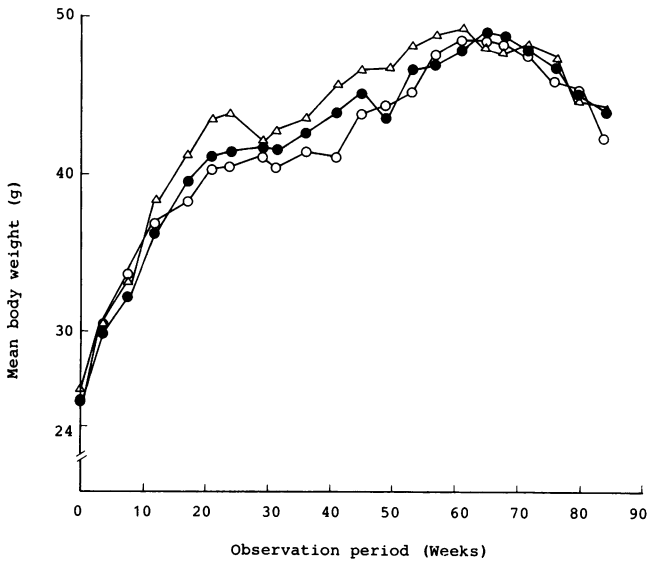

FIGURE 2. Growth curves of male B6C3F1 mice given sodium chlorite in drinking water at concentrations of 0 (control) (○—○), 0.025 (●—●), or 0.05% (△—△).

the study for a mouse from each group, were 658 and 1067 mg/mouse in the low dose group, and 1261 and 1606 mg/mouse in the high dose group for females and males, respectively.

Survival

Survival curves for the control and treated groups of female and male mice are shown in Figures 3 and 4, respectively. There was no dose-related trend in mortality over the experimental period in the control and other treated groups for females and males. Male mice in the control group were lost mainly due to fighting after 34 weeks. The percentages of mice surviving at week 85 were as follows: females—control, 47/50 (94%); low dose, 50/50 (100%); high dose, 50/50 (100%); males—control, 35/50 (70%); low dose, 47/50 (94%); high dose, 43/50 (86%).

Organ Weights

Organ weights and percent organ to body weight ratio for each group of both sexes are shown in Table 1. No significant increases with dose dependency were seen in any organ weight and percent organ to body weight ratio of both females and males treated with sodium chlorite compared to control groups.

Histopathological Findings

Tumor distribution and incidence in each group of both sexes are shown in Table 2. Mice surviving 85 weeks were included in the effective number. The incidence of tumor-bearing animals were as follows: females—control, 15/47 (32%); low dose, 17/50 (34%); high dose, 13/50 (26%); males—control, 16/35 (46%); low dose, 27/47 (57%); high dose, 23/43 (53%). Tumors developed in the liver, lung, hematopoietic system, Harderian gland, spleen, subcutis, pituitary, thyroid, and ovary in the control and each treated group. Histologically, the lesions of the liver were classified as hyperplastic nodule, hepatocellular carcinoma, and hemangioma. Hyperplastic nodules were sharply demarcated lesions, which showed proliferation of hepatocytes. They were as large as or larger than the area of several lobules. The cells, having enlarged and hyperchromatic nuclei and prominent nucleoli, varied in size and were arranged as single or double layers in plates. Hepatocellular carcinomas had a trabecular structure with cellular or nuclear atypism. Some of these lesions metastasized to the lung; one case occurred in both the low

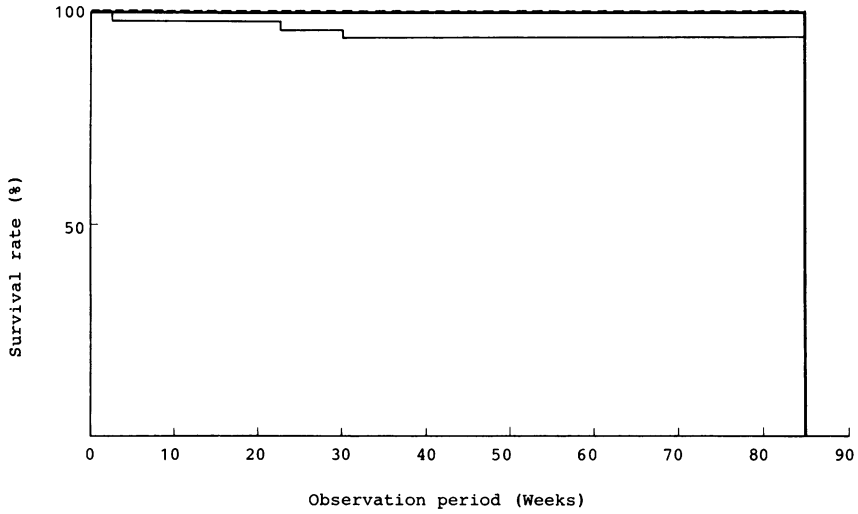

FIGURE 3. Survival rates of female B6C3F1 mice given sodium chlorite in drinking water at concentrations of 0 (control) (——), 0.025 (——), or 0.05% (---).

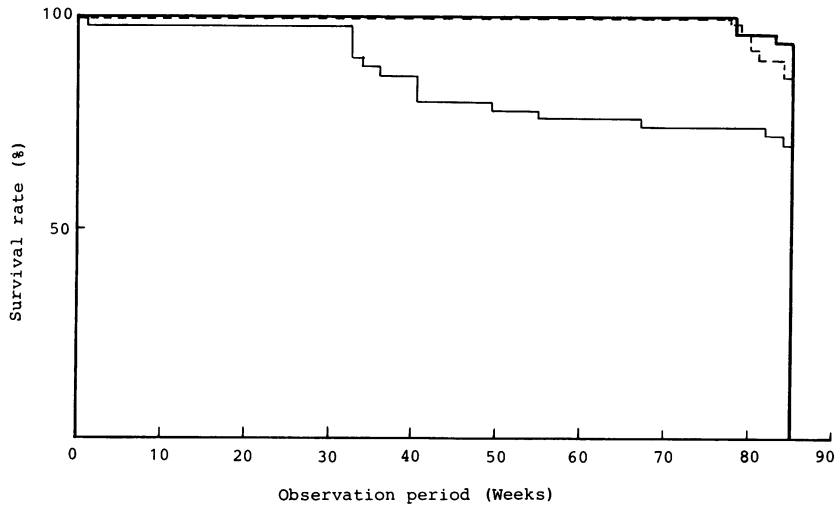

FIGURE 4. Survival rates of male B6C3F1 mice given sodium chlorite in drinking water at concentrations of 0 (control) (——), 0.025 (——), or 0.05% (---).

and the high dose group of males. Lesions more frequently encountered in each group of male mice were hyperplastic nodules and hepatocellular carcinomas; however, no significant differences were found between control and treated groups. Hemangiomas were observed sporadically in the low dose group of female mice.

Histologically, the lesions of the lung were classified into adenomas and adenocarcinomas. The incidence of adenomas in the high dose group of males was significantly higher than that of the control group. No significant differences were found in the incidence of adenocarcinomas between control and treated groups of both sexes.

Malignant lymphomas/leukemias were frequent in the control group of both sexes, but their incidence was significantly lower in the high dose group of females. Peripheral blood samples stained by Giemsa showed the appearance of lymphoblast cells. However, abnormalities of red blood cells, including acanthocytes, were not observed. The incidence of tumors in other organs, e.g., Harderian gland, spleen, subcutis, pituitary, thyroid, and ovary, were not significantly different from those of controls of both sexes in any of the three groups.

Nonneoplastic lesions in various organs were infrequent, and no significant differences in the incidence between control and treated groups were found.

Discussion

According to previous reports (*19–21*), the most common neoplasms that occurred spontaneously in B6C3F1 male mice during the observation period of 79 to 104 weeks were hyperplastic nodules of the liver (the incidence was 7.9–28.2%), hepatocellular carcinoma (13.7–19.6%), lymphomas/leukemias (4.3–12.8%), and pulmonary adenomas (2.2–7.7%) and carcinomas (2.1–6.5%). In female mice, common tumors were lymphomas/leukemias (16–25%), pulmonary adenomas (2.1–4.4%) and carcinomas (0–2.1%), hyperplastic nodules of

Table 1. Final body weights and organ weights of B6C3F1 mice given sodium chlorite in drinking water.

Dose, %	Sex	No. of mice examined	Body weight, g		Organ weight, g[a] (% of body weight)						
			Initial	Final	Lung	Liver	Pancreas	Kidney	Spleen	Heart	Brain
0	F	47	20.0 ± 1.0	48.4 ± 3.7	0.36 ± 0.21 (0.71)	1.54 ± 0.34 (3.18)	0.33 ± 0.07 (0.68)	0.46 ± 0.27 (0.95)	0.17 ± 0.19 (0.35)	0.13 ± 0.03 (0.27)	0.44 ± 0.03 (0.91)
	M	35	25.6 ± 1.1	40.3 ± 2.5	0.40 ± 0.10 (0.99)	1.95 ± 0.73 (4.8)	0.43 ± 0.81 (1.07)	0.67 ± 0.10 (1.66)	0.18 ± 0.27 (0.45)	0.21 ± 0.05 (0.52)	0.46 ± 0.05 (1.14)
0.025	F	50	19.9 ± 0.3	50.8 ± 2.5	0.44 ± 0.13 (0.87)	1.70 ± 0.42 (3.35)	0.38 ± 0.14 (0.75)	0.48 ± 0.09 (0.94)	0.24 ± 0.54 (0.47)	0.17 ± 0.03 (0.33)	0.46 ± 0.03 (0.91)
	M	50	25.5 ± 0.6	40.3 ± 2.0	0.38 ± 0.07 (0.94)	2.06 ± 1.12 (5.11)	0.36 ± 0.10 (0.89)	0.65 ± 0.08 (1.61)	0.13 ± 0.10 (0.32)	0.21 ± 0.03 (0.52)	0.44 ± 0.05 (1.09)
0.05	F	50	19.4 ± 0.4	47.4 ± 3.9	0.38 ± 0.09 (0.80)	1.58 ± 0.49 (3.33)	0.37 ± 0.44 (0.78)	0.45 ± 0.06 (0.95)	0.25 ± 0.41 (0.53)	0.15 ± 0.03 (0.31)	0.44 ± 0.05 (0.93)
	M	50	26.0 ± 0.1	42.7 ± 1.2	0.43 ± 0.15 (1.10)	2.33 ± 1.28 (5.47)	0.40 ± 0.12 (0.94)	0.66 ± 0.09 (1.55)	0.16 ± 0.16 (0.37)	0.21 ± 0.03 (0.49)	0.43 ± 0.05 (1.01)

[a] Values represent average ± SD.

Table 2. Tumor distribution and incidence in B6C3F1 mice given sodium chlorite in drinking water.

Dose, %	Sex	Effective no. of mice[a]	No. of tumor bearing mice, %	Tumor distribution and incidence, %												
				Liver			Lung		Harderian Spleen		Subcutis		Pituitary	Thyroid	Ovary	MLY/LEU
				HN	HCC	H	A	AC	T	H	FS	MFH	A	A	PA	
0	F	47	15(32)	5(11)	0 (0)	0(0)	3 (6)	0(0)	2(4)	0(0)	0(0)	0(0)	2(4)	0(0)	0(0)	7(15)
	M	35	16(46)	6(17)	4(11)	0(0)	0 (0)	0(0)	1(3)	1(3)	0(0)	0(0)	0(0)	0(0)		4(11)
0.025	F	50	17(34)	3 (6)	1 (2)	1(2)	1 (2)	1(2)	4(8)	0(0)	0(0)	0(0)	0(0)	1(2)	1(2)	5(10)
	M	47	27(57)	14(30)	8(17)	0(0)	2 (4)	1(2)	3(6)	0(0)	2(4)	0(0)	0(0)	0(0)		2(4)
0.05	F	50	13(26)	5(10)	1 (2)	0(0)	2 (4)	0(0)	4(8)	1(2)	0(0)	0(0)	0(0)	0(0)	0(0)	1 (2)[b]
	M	43	23(53)	11(26)	6(14)	0(0)	5(12)[b]	2(5)	1(2)	0(0)	1(2)	1(2)	0(0)	0(0)		1 (2)

HN, hyperplastic nodule; HCC, hepatocellular carcinoma; H, hemangioma; A, adenoma; AC, adenocarcinoma; MLY/LEU, malignant lymphoma/leukemia; T, tumor; FS, fibrosarcoma; MFH, malignant fibrous histiocytoma; PA, papillary adenoma.

[a] Based on histological examination of mice sacrificed 85 weeks after the beginning of the experiment.

[b] $p < 0.05$ against 0% group.

the liver (1.1–4.4%) and carcinomas (1.8–4.4%), and pituitary adenomas (3–8.3%).

In the present study, the neoplasms that occurred frequently in each group of both sexes were similar to those mentioned above; however, the incidence of pulmonary adenoma in the high dose group of males was higher than the incidence of spontaneous tumors reported, and the incidence of lymphomas/leukemias in the high dose group of females was lower. The present result showing a significantly higher incidence of lung adenomas in the high dose group of males might either be attributed to a statistical variation resulting from the too low adenoma incidence in control males, or make a strong case for further intensive studies on the carcinogenicity of sodium chlorite. In any case, taking into account of the absence of dose-related increases in the incidences of lung adenomas and the lack of increased incidences of lung adenocarcinomas, it would not be possible from our present results to conclude a carcinogenic potential of sodium chlorite for the lung in mice. In this context, reportedly, chlorite preferably distributes to the blood, testis, and lung after the oral administration in rats (*22*). Further, a weak promoting activity of sodium chlorite has been reported in two-stage skin carcinogenesis in Sencar mice (*16*). Further studies would be required to conclude the carcinogenicity of this substance.

Moore et al. (*23*) reported that chlorite produced increases in osmotic fragility, mean corpuscular volume and glucose-6-phosphate dehydrogenase activity of red blood cells, and number of acanthocytes in A/J and C57L/J mice on exposure to a dose of 100 ppm in drinking water for 30 days. The morphological distortions in erythrocytes have also been reported in the rat and chicken (*24*). In the present study, no alteration was observed in erythrocyte morphology even in the high dose groups (500 ppm) of both sexes.

Because sodium chlorate caused toxic damage to the kidneys (*9*), it has been postulated that chlorite, because of its more potent oxidant capabilities (*14,15*), may be potentially more harmful to the kidney. Recently, Moore et al. (*12,23*) and Connor et al. (*25*) reported the lack of the nephrotoxicity of sodium chlorite in mice and rats; sodium chlorite was administered orally in drinking water for 180 days at a concentration up to 100 ppm in mice and 500 ppm in rats. Our present study was performed at five times higher dose and three times longer periods than those in previous reports (*12,22,24*). Nevertheless, no effects were produced in the kidney by sodium chlorite. Therefore, our present data confirm previous reports that no significant difference existed in the mean kidney weights and the percent kidney to body weight ratio between control and treated groups, and, moreover, histological examination did not reveal any detectable toxic damage to the kidneys of each treated group of both sexes.

Abdel-Rahman et al. (*26*) reported that administration of chlorine dioxide and/or its by-products to rats in drinking water for 3 months interfered with DNA synthesis at high doses in the intestinal mucosa and at lower doses in testes and liver. The significance of these results is presently obscure; however, it is interesting to note whether or not the apparent depression of DNA synthesis in the testes is associated with depressed spermatogenesis and reproductive toxicity in the male rat (*27*). In the present study, no remarkable histological changes of the testes and intestine were observed in any of the treated groups.

In the present study, clear evidence of carcinogenic activities of sodium chlorite in B6C3F1 mice was not observed. However, considering that this substance is widely used as an environmental chemical, further experimental studies will be necessary to identify and quantify more clearly the hazards of this substance.

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